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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|----------------------------|------------------------|
| 10/048,013 | 04/29/2002 | Michael Luconi | LUCONI1 | 1351 |
| 1444 7590 09/21/2007 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303 | | | EXAMINER WOOD, AMANDA P | |
| | | | ART UNIT 1657 | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|-----------------|---------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/048,013 | LUCONI ET AL. | |
| | Examiner | Art Unit | |
| | Amanda P. Wood | 1657 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 June 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4, 5, 9, 12, 19 and 20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4, 5, 9, 12, 19 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response and amendment filed 11 June 2007 has been received and entered.

Claims 1, 4, 5, 9, 12, 19 and 20 have been considered on the merits.

Claim Rejections - 35 USC § 103

Claims 1, 4, 5, 9, 12, 19 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nass-Arden et al (Mol. Reprod. Dev. 1990) in view of Vlahos et al (J. of Biol. Chem. 1994) for the reasons set forth in the previous office action which are restated below.

Nass-Arden et al teach a method wherein mammalian sperm (i.e., seminal liquid comprising spermatozoa) is treated with quercetin (i.e., an inhibitor of phosphatidylinositol 3-kinase) so as to increase the motility of the sperm. Nass-Arden et al further teach a method wherein the sperm are separated by sperm separation methods used in ART (i.e., assisted reproduction techniques), such as the wash and spin method, the sedimentation method, or the pellet and swim-up method. Furthermore, Nass-Arden et al teach that in the first two hours of treatment with quercetin, motility is inhibited in sperm, but afterward, motility intensity and duration is enhanced. In addition, Nass-Arden et al teach that untreated sperm show no motility after 3.5 hours, whereas the sperm treated with the phosphatidylinositol 3-kinase inhibitor quercetin show high motility at this point, and continue to show high motility for an additional 2-3 hours. Furthermore, Nass-Arden et al teach that quercetin might be a good candidate to increase the fertilizing potential of spermatozoa (see, for example, Abstract, pg. 369, col. 2, pg. 370, col. 1, col. 2, and pg. 373, col. 1).

Vlahos beneficially teach that phosphatidylinositol 3-kinase has been suggested to play a role in cell motility in response to growth factors or chemotactic agents (see, for example, , pg.

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5241, col. 2). Vlahos et al beneficially teach that quercetin is a known inhibitor of phosphatidylinositol 3-kinase that is directed at the ATP-binding site of the kinase. Vlahos et al also beneficially teach that quercetin has also been shown to inhibit other phosphatidylinositols and protein kinases, which can be an unwanted side effect of using this particular inhibitor. For this reason, Vlahos et al teach that it would be beneficial to find other inhibitors of phosphatidylinositol 3-kinase that do not affect phosphatidylinositol 4-kinase or other selected protein kinases. Vlahos et al beneficially teach that 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one, or (LY294002), completely and specifically abolished phosphatidylinositol 3-kinase activity but did not inhibit any other tested protein or lipid kinases. Vlahos et al beneficially teach that LY294002 was efficacious in inhibiting phosphatidylinositol 3-kinase activity in whole cell assays (e.g., human neutrophils) as well as in purified phosphatidylinositol 3-kinase (see, for example, Abstract, pg. 5247, col. 2).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method disclosed by Nass-Arden et al based upon the beneficial teachings provided by Vlahos et al, with respect to the art-recognized method of substituting one inhibitor for a more specific inhibitor, in particular LY294002, and the fact that inhibitors of phosphatidylinositol 3-kinase for use in humans are well known in the art, as discussed above. Furthermore, Vlahos et al particularly teach that quercetin is a known inhibitor of phosphatidylinositol 3-kinase, which has been suggested to have a role in cell motility, and that it also inhibits other enzymes, which is an undesirable side effect. Vlahos et al further point out that it would be beneficial to find inhibitors of phosphatidylinositol 3-kinase that do not affect any other enzymes, and therefore, Vlahos et al teach that LY294002 is a specific inhibitor of phosphatidylinositol 3-kinase that is effective in whole-cell assays using human neutrophils. In

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addition, Nass-Arden et al beneficially teach that quercetin-treated sperm have greater motility for longer duration than untreated sperm, and that treatment with such a compound may increase the fertilizing potential of spermatozoa, and therefore, it would have been both obvious and beneficial for the skilled artisan to modify the methods taught by Nass-Arden et al to treat human sperm with a specific PI3K inhibitor so as to increase their motility for use in ART procedures. Based upon the beneficial teachings of Nass-Arden et al and Vlahos et al, it would have been obvious to one of ordinary skill in the art to treat human seminal fluid comprising spermatozoa with a phosphatidylinositol 3-kinase inhibitor such as LY294002, or derivatives thereof and to use a method well-known in ART to separate the spermatozoa. Furthermore, based upon the knowledge that treatment of sperm with a PI3K inhibitor increases the motility of normal sperm, one of ordinary skill in the art would have had a reasonable expectation of success of increasing the motility of abnormal sperm for the expected benefit of increasing the fertilization potential of said sperm, whether for use in ART procedures or for animal husbandry. The result-effective adjustment of particular conventional working conditions (e.g., using a particular amount of a particular phosphatidylinositol 3-kinase inhibitor and/or using a particular method of separation or ART therapy) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Response to Arguments

Applicant's arguments filed 1 June 2007 have been fully considered but they are not persuasive. Applicant argues that one of skill in the art would not have been motivated to use the PI3K inhibitor LY294002 to enhance sperm motility based upon the teachings of Vlahos et al, because Vlahos et al only teach that this specific PI3K inhibitor works differently from quercetin and is an anti-proliferative agent. The Examiner respectfully disagrees with

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Applicant's arguments, because, in particular, Vlahos et al also teach that PI3K is involved in cell motility, in addition to cell proliferation, and that the specific inhibitor of PI3K, LY294002, abolishes PI3K activity in human neutrophils (i.e., in human cells). Furthermore, Vlahos et al teach that products of PI3K are involved in actin polymerization. In addition, Applicant argues that Nass-Arden et al do not teach a method using human sperm. One of ordinary skill in the art would have expected such methods as those provided by Nass-Arden et al, which work on normal sperm of mammals used in animal husbandry techniques, to be useful on both normal and abnormal sperm of humans in ART. Therefore, based upon the teachings of Nass-Arden et al in view of Vlahos et al, it would have been obvious to provide the instantly claimed method for increasing spermatozoa motility.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda P. Wood whose telephone number is (571) 272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

APW
Examiner
Art Unit 1657

APW


RALPH GITOMER
PRIMARY EXAMINER
GROUP 1200